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Serum parathyroid hormone level is elevated in some patients with disorders of keratinization.

Milstone LM, Ellison AF, Insogna KL.

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BACKGROUND AND DESIGN--After the chance of observation of an elevated parathyroid hormone (PTH) value in a patient with pityriasis rubra pilaris, the serum PTH level was measured in the next 14 patients seen with disorders of keratinization. Calcium metabolism in three affected patients was then studied in depth. RESULTS--Five of 15 patients had twofold or greater elevations in serum PTH values. The patients had four different disorders of keratinization: bullous congenital ichthyosiform erythroderma (two patients); lamellar ichthyosis (one patient); pityriasis rubra pilaris (one patient); and ichthyosis linearis circumflexa (one patient). At least one other patient with each diagnosis had normal PTH values. Two of three patients who were studied further had clear evidence of increased, biologically active PTH, consistent with secondary hyperparathyroidism. An elevated PTH level spontaneously became normal in one patient, and in a second patient it became normal with a high-calcium diet. CONCLUSIONS--These data provide the first indication that patients with various disorders of keratinization have an increased risk for secondary hyperparathyroidism. The exact prevalence, origin, and physiologic significance of this finding remain to be elucidated.

PMID: 1320849 [PubMed - indexed for MEDLINE]

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1: Arch Dermatol. 1995 May;131(5):556-60.

Efficacy, tolerability, and safety of calcipotriol ointment in disorders of keratinization. Results of a randomized, double-blind, vehicle-controlled, right/left comparative study.

Kragballe K, Steijlen PM, Ibsen HH, van de Kerkhof PC, Esmann J, Sorensen LH, Axelsen MB.

Department of Dermatology, University Hospital Aarhus, Denmark.

BACKGROUND AND DESIGN: Disorders of keratinization are a heterogeneous group of diseases that have in common a defect in cornification. The bioactive form of vitamin D3 has been shown to modulate epidermal proliferation and differentiation. The purpose of the present study was to determine the effect of the synthetic vitamin D3 calcipotriol in a randomized, double-blind, placebo-controlled, right/left comparative study. The 67 patients included in the study were at least 12 years of age and had the following diseases: ichthyosis vulgaris (n = 9), X-linked ichthyosis (n = 8), congenital ichthyosis (n = 10), hereditary palmoplantar keratoderma (n = 20), keratosis pilaris (n = 9), and Darier's disease (n = 11). Calcipotriol ointment (50 micrograms/g) and placebo (vehicle of calcipotriol ointment) were applied to all patients twice daily for up to 12 weeks. The patients were allowed to use up to 120 g of calcipotriol ointment per week. RESULTS: At the end of the treatment regimen, calcipotriol ointment had an effect on the improvement of the ichthyoses, although to a variable degree. No therapeutic effect was detected in palmoplantar keratoderma or keratosis pilaris. Eight of 12 patients with Darier's disease had to be withdrawn because of skin irritation or a worsening of the disease. Skin irritation occurred in 18 cases (26%) only on the calcipotriol-treated side, and in one case (1%) only on the placebo-treated side. Nine cases (13%) had irritation on both sides. The amount of calcipotriol ointment used per week was lowest in palmoplantar keratoderma (mean, 11.8 g/wk; range, 2.1 to 25.6 g/wk) and highest in congenital ichthyosis (mean, 59.3 g/wk; range, 11.4 to 94.7 g/wk). There was no clinically significant change of serum calcium levels during the treatment period. CONCLUSION: Short-term treatment with calcipotriol ointment (50 micrograms/g) used in amounts up to about 100 g/wk is moderately efficacious, well-tolerated, and safe in adult patients with various ichthyoses.

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British Journal of Dermatology (1993) **129**, 547–554.

Barrier function parameters in various keratinization disorders: transepidermal water loss and vascular response to hexyl nicotinate

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Summary In this study, we characterized the stratum corneum barrier function in 39 patients with various keratinization disorders (autosomal dominant ichthyosis vulgaris [ADI] [$n=7$], X-linked recessive ichthyosis [XRI] [$n=6$], autosomal recessive congenital ichthyosis [CI] [$n=10$], dyskeratosis follicularis [Darier's disease; DD] [$n=8$], erythrokeratoderma variabilis [EKV] [$n=8$]), and 21 healthy volunteers, using two non-invasive methods: transepidermal water loss (TEWL) measuring outward transport of water through the skin by evaporimetry, and the vascular response to hexyl nicotinate (HN) penetration into the skin as determined by laser-Doppler flowmetry.

Significantly increased TEWL values were found on the volar forearm in all three forms of ichthyosis, compared with the healthy control group, with the highest TEWL values in the CI group. The penetration of HN on the volar forearm was accelerated in patients with ADI, XRI and CI, as indicated by a shorter lag time (t_{l0}) between HN application and initial vascular response. However, differentiation between CI and the other ichthyoses was not possible by this method. When using both methods in DD and EKV, no differences compared with the healthy controls could be detected on the volar forearm, where the skin was principally unaffected; only the measurements from the affected skin on alternative sites demonstrated significantly increased TEWL values. In ADI and CI, however, normal-appearing skin also showed impaired values.

We conclude that both TEWL and the vascular response to penetration of HN are suitable methods to monitor the skin barrier function in keratinization disorders, and are helpful in discriminating between these disorders.

The barrier function of the skin can be characterized by two complementary methods: (i) the evaporation of water from the skin measured as transepidermal water loss (TEWL),[1] and (ii) the assessment of penetration of various substances (e.g. esters of nicotinic acid[2] and benzoic acid[3]) into the skin. We used hexyl nicotinate (HN), because after crossing the epidermis it induces vasodilatation as a physiological response. Vasodilatation increases cutaneous blood flow (CBF), which can be measured by laser-Doppler flowmetry (LDF). If the barrier function is impaired, a faster and more pronounced LDF response can be expected. Both methods, TEWL and HN penetration, are reproducible and reliable when performed under standardized conditions.[4]

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We studied the barrier function of the skin in three types of ichthyosis, namely autosomal dominant ichthyosis (ADI), X-linked recessive ichthyosis (XRI), and autosomal recessive congenital ichthyosis (CI). The ichthyoses are a heterogeneous group of hereditary keratinization disorders characterized by a 'dry', scaly appearance of the skin. More than 20 well-established genetic entities have been described.[5] Using clinical and histological criteria, it remains difficult to distinguish between individual forms of ichthyosis, especially between ADI and XRI.[6] Various forms of ichthyosis are known to be associated with an impaired barrier function of the skin,[7–9] which is characterized by an increased diffusion of water through the skin.

Two other keratinization disorders were also investigated; dyskeratosis follicularis (Darier's disease; DD) and erythrokeratoderma variabilis (EKV), both of which are

Table 1. Details of test subjects

	n	Sex F/M	Age (years) mean (range)	Atopic constitution	Acitretin therapy
Patients (total)	39	19/20	33 (14–70)	8	16
ADI	7	3/4	31 (14–51)	4	0
XRI	6	0/6	36 (17–70)	2	0
CI	10	8/2	30 (17–46)	0	5
DD	8	5/3	39 (17–61)	1	5
EKV	8	3/5	31 (17–55)	1	6
Healthy volunteers (controls)	21	11/10	34 (17–65)	6	0

ADI, autosomal dominant ichthyosis vulgaris; XRI, X-linked recessive ichthyosis; CI, autosomal recessive congenital ichthyosis; DD, dyskeratosis follicularis; EKV, erythrokeratoderma variabilis.

genodermatoses with an autosomal dominant mode of inheritance. To our knowledge, no information is available on the barrier function of the skin in DD and EKV patients.

The aims of the present study were the following: firstly, to establish the differences with respect to the barrier function of the skin between different keratinization disorders and normal skin, and secondly, to compare the two methods, TEWL and vascular response to HN, with respect to their correlation and discriminatory power.

Methods

Test subjects

We tested 39 patients with keratinization disorders (different types of ichthyosis, Darier's disease and erythrokeratoderma), and 21 healthy volunteers without skin disease (skin types 2 and 3) [Table 1]. The diagnosis of X-linked ichthyosis was confirmed in six patients by determination of the steroid sulphatase levels in leucocytes.[10] The congenital ichthyosis (CI) group consisted of 10 patients with autosomal recessive congenital ichthyosis, of whom eight had the clinical phenotype of non-erythrodermic lamellar ichthyosis, and two had the clinical phenotype of erythrodermic lamellar ichthyosis (also known as congenital ichthyosiform erythroderma). The test sites were assessed and graded as normal-appearing, and affected.

Sex- and age-distribution were similar in the entire patient group and the controls (Table 1). Eight patients and six healthy subjects had a history of allergic rhinitis/conjunctivitis or asthma, but none suffered from atopic dermatitis. Sixteen patients with CI, DD and EKV were treated with acitretin in various dosages, and continued to take the drug during measurements (Table 1). All measurements were performed during the months of November and December 1991. The use of topical treatments and topical cosmetics on the test sites was discontinued in patients and controls 1 week before the measurements.

Transepidermal water loss

Transepidermal water loss was measured using an evaporimeter (EP1, ServoMed, Stockholm, Sweden), as previously described in detail.[4] Room temperature was maintained at 19·5–22·5°C, and humidity varied between 44 and 59%. The measurements were performed at a skin surface temperature between 27·6 and 32·8°C.

Because previous studies have reported regional variation in baseline TEWL,[3,11,12] and an increase of TEWL from the proximal to the distal forearm,[3,11] we measured TEWL at a defined distance, 8 cm distal to the flexural creases of the elbows, on the left and right volar forearms. Measurements were also performed on the dorsal forearms (opposite the volar measuring site), because the clinical appearance can differ between volar and dorsal forearms in the various types of ichthyosis studied. If in DD or EKV there was no clinically abnormal skin on these sites, we performed an additional measurement of TEWL on one affected body site. TEWL was measured on the same sites in healthy controls. The number of different anatomical sites was limited.

Vascular response to hexyl nicotinate penetration as assessed by laser-Doppler flowmetry

An increased CBF induced by HN was measured by LDF [Diodopp Applied Laser Technology, Maarheeze, The Netherlands] as previously described.[4] Briefly, baseline CBF on the untreated volar forearms was recorded for a period of 3 min. Subsequently, 20 μl of 10 mM HN [Sigma, St Louis, MO, U.S.A.] in a 60:40 propylene glycol/isopropanol vehicle was applied to the left volar

forearm using an absorbent filter-paper disc (1 cm in diameter). After 30 s the saturated paper disc was removed, excess solution was wiped off, and CBF was assessed continuously until a clear maximum response, followed by a plateau phase, was achieved. The following parameters were derived from the recording: the baseline CBF (LDF_{bas}); the lag time between application and initial response in seconds (t_0); the time between application and maximum response in seconds (t_{max}); the maximum response (LDF_{max}); the slope of the curve between t_0 and t_{max} per minute (slope). The vehicle was tested on the right volar forearm using the same test procedure.

Statistical analysis

Comparison of each parameter between the different groups was performed with a one-way analysis of variance (ANOVA). In case of significant differences ($P<0.05$), Fisher's LSD (least square difference) method was used for further analysis. Comparison of two groups was by unpaired Student's *t*-test. Paired data were analysed by Student's *t*-test. Correlations were studied with Pearson's correlation coefficient.

Results

1 *Transepidermal water loss*

Patients compared with healthy controls (left volar forearm)

The results of TEWL measurements from the volar forearm in patients and controls are shown in Figure 1. The mean TEWL values were significantly increased in all three forms of ichthyosis, compared with the healthy control group ($P<0.05$). There were no significant differences between DD or EKV and the healthy control group. TEWL values on the volar site were significantly higher in CI than in the other patient groups ($P<0.05$). There were no significant differences between the other disorders. With the exception of one observation, all values in the CI group exceeded the upper limit of the normal range (7·6 g/m²/h). As shown in Figure 1, the clinical appearance of the skin at one location in one disease group did not seem to influence the TEWL.

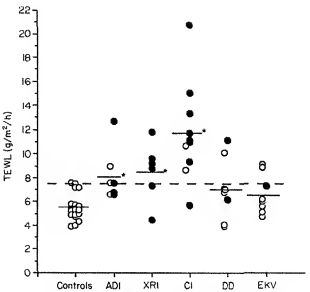

Figure 1. TEWL values measured on the left volar forearm, in relation to the severity of the skin disorder. ○, normal-appearing skin; ●, affected skin; ——, mean values; - - -, upper limit of the normal TEWL range; * significantly different at a 5% level in the ANOVA compared with the control group.

Dependence on different anatomical sites

Volar and dorsal sites on the left forearm. As the severity of the clinical signs differs in the various types of ichthyosis between the volar and dorsal forearms, TEWL was also measured on the dorsal forearm. In ADI there was a

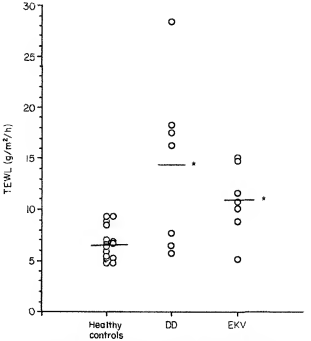

Figure 2. TEWL values measured on affected alternative sites in DD and EKV patients. ——, mean values; * significantly different at a 5% level in the ANOVA compared with the control group.

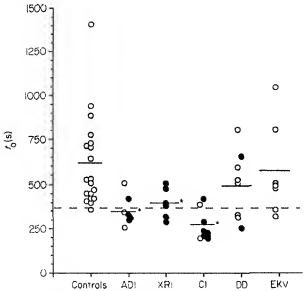

Figure 3. Lag time (t_{l0}) after hexyl nicotinate application, measured on the left volar forearm, in relation to the severity of the skin disorder. ○, normal-appearing skin; ●, affected skin; ——, mean values; - - -, lower limit of the normal t_{l0} range; * significantly different at a 5% level in the ANOVA compared with the control group.

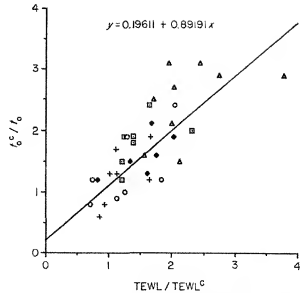

Figure 4. Comparison between TEWL and lag time (t_{l0}) (measured on the left volar forearm), with regard to their discriminatory value.

$$\text{TEWL/TEWL}^c = \frac{\text{TEWL values of the individual patients}}{\text{mean TEWL value of the control group}}$$

$$t_{l0}{}^c/t_{l0} = \frac{\text{mean } t_{l0} \text{ value of the control group}}{t_{l0} \text{ values of the individual patients}}$$

□, ADI; ◆, XRI; △, CI; ○, DD; ▽, EKV.

Table 2. Parameters of the vascular response to hexyl nicotinate penetration, as measured by laser-Doppler flowmetry (LDF) on the left volar forearm (values are expressed as means; SEM in parentheses)

Group	n	LDF_{bas}	t_{max} (s)	LDF_{max}	Slope (min^{-1})
ADI	7	17·9 (1·3)	681 (95)*	175 (12)	54 (10)*
XRI	6	27·0 (1·4)	851 (35)	205 (27)	26 (7)
CI	9	62·8 (20·0)*	599 (56)*	302 (67)*	65 (8)*
DD	8	18·1 (4·0)	953 (108)	155 (19)	33 (7)
EKV	7	21·3 (3·3)	976 (139)	151 (23)	33 (8)
Controls	20	19·7 (2·3)	1067 (68)	168 (13)	32 (3)

* Comparison of patients with controls: significantly different at a 5% level in the ANOVA.

ADI, autosomal dominant ichthyosis vulgaris; XRI, X-linked recessive ichthyosis; CI, autosomal recessive congenital ichthyosis; DD, dyskeratosis follicularis; EKV, erythrokeratoderma variabilis.

tendency for TEWL values on dorsal sites (mean 9·9 g/m^2/h) to be higher than on volar sites (mean 8·1 g/m^2/h), but no significant differences were found.

Other locations. On the volar forearm, in most cases of DD (6/8) and EKV (7/8), only normal-appearing skin, with normal TEWL values, was found. Therefore, in these patients TEWL measurements were also performed on one of the following affected body sites: dorsal elbow, dorsal upper arm, flexural crease of the elbow, ventral shoulder. TEWL was measured on the same sites (Fig. 2) in healthy controls. Significantly increased TEWL values ($P<0·05$) were found in the DD and EKV groups compared with the healthy controls.

Effect of age, sex, atopy, skin temperature and acitretin therapy

No significant differences in TEWL values were noticed between males and females in the whole patient group, or in controls. No correlation was detectable between TEWL and age ($r=-0·15$ in the control group; $r=-0·08$ in the whole patient group). A history of atopy had no influence on TEWL values in the control and patient groups. No correlation was detectable between skin temperature and TEWL in healthy controls ($r=0·10$), the total patient group ($r=0·24$), or the entire study group ($r=0·04$). Therefore, no temperature correction of the TEWL values was performed. Acitretin therapy had no effect on TEWL values in the various patient groups.

2 Hexyl nicotinate penetration

Three of the 60 test subjects did not react within 30 min after HN application (non-responders). Of these three, one was in the control group, one in the CI group (this was the same subject who showed a normal TEWL value), and one in the EKV group. Further analyses were therefore restricted to 57 subjects.

LDF measurements: patients compared with healthy controls

By analysing the LDF profile, a significant decrease in the lag time (t_0) was found in the three forms of ichthyosis, compared with the control group ($P<0.05$) [Fig. 3]. Comparison between patient groups showed significant differences between CI and DD/EKV ($P<0.05$), but not between CI and the other types of ichthyosis. The other LDF profile parameters were less discriminating (Table 2). The t_{max}, and the slope, showed significant differences between CI and controls ($P<0.05$), and between ADI and controls ($P<0.05$). LDF_{bas} and LDF_{max} showed only differences between CI and controls (Table 2).

The vehicle applied as a control to the right volar forearm did not increase the cutaneous blood flow, except in four CI patients. In these patients, there was only a slight CBF increase (1·2–1·4-fold) after vehicle application, in contrast with the marked increase after HN application (2·4–5·2-fold). Furthermore, there was a considerably longer time lag (mean 318 s) after vehicle application than after HN application (mean 212 s).

Effect of age, sex, atopy and acitretin therapy

Age and atopic constitution did not influence the lag time values (t_0). Significantly longer lag times were found in male patients than in female patients (mean t_0: males, 479 s; females, 342 s; $P=0.02$). This finding may be explained by the high number of females in the CI group (8/10), and by the fact that the shortest lag times were found in CI. However, the same trend was seen in the control group (mean t_0: males, 711 s; females, 528 s; $P=0.11$). There was no apparent influence of acitretin therapy on t_0 values in the various patient groups.

3 Correlation and comparison between TEWL and t_0

There was a negative correlation between TEWL and t_0 in the patient group ($r=-0.64$) and in the control group ($r=-0.31$).

To establish the discriminatory value of each method, the TEWL values of the patients were divided by the mean TEWL value in the healthy controls, and were plotted against the mean t_0 value of the controls divided by the patients' t_0 values (Fig. 4). This normalized plot would theoretically yield a straight line with a slope of 1·0 if the discriminatory power of both methods was exactly the same. A slope of greater than 1·0 would reflect a superiority of LDF (t_0), and a slope less than 1·0 a superiority of TEWL. The slope of the line was 0·89.

Discussion

In characterizing the barrier properties of the skin, TEWL was shown to be a good parameter to discriminate between the skin of patients with various keratinization disorders and that of healthy volunteers. All three forms of ichthyosis showed a significantly increased TEWL compared with controls. The TEWL values in the control group are in agreement with published normal mean values, which vary between 2·8 and 6·5 $g/m^2/h$.[11] TEWL in CI was significantly increased compared with ADI and XRI, which made it possible to discriminate between CI and the other two forms of ichthyosis. Increased TEWL values have been described in ichthyosis patients previously.[7–9] Frost[7] studied the same three types of ichthyosis, and reported a 1·2–1·4-fold increase in TEWL compared with controls. He could not discriminate between the three types of ichthyosis. Grice[8] measured TEWL in seven patients with XRI and two with ADI, and found an approximately twofold increase in TEWL compared with a control group. It is difficult to compare our results with the data of Frost and Grice, because they measured TEWL with a closed chamber technique. Using an evaporimeter in three patients with CI, Kilstala[9] found TEWL values comparable with those in our study (10, 10 and 18 $g/m^2/h$).

The skin barrier function on the volar forearm was also studied by measuring the vascular response to HN penetration (as assessed by LDF). Among the various LDF parameters assessed in the present study, t_0 values showed results similar to those seen with TEWL values. The decreased lag time found in the disease states can be explained by an acceleration of the penetration of HN due to impaired barrier function of the skin. The other parameters were less useful in discriminating between the different diseases. This is an expected finding, as the lag time is the paramcter which is most dependent on the barrier quality, and least dependent on the vasoreactivity. Kohli[14] also recommended the lag time (t_0) as the most relevant LDF parameter, because he observed that t_0 is strictly dependent on the HN dose used.

The weak reaction to the vehicle found in four CI

patients can be explained by an irritant response to propylene glycol and isopropanol. This effect seems to be small, because the reaction was weak compared with that seen after HN penetration. Vehicle influences on the LDF profile resulting from penetration of nicotinates have been described.[14]

A limitation of the vascular response to HN penetration (as assessed by LDF) is that it depends on the skin barrier quality as well as on the vascular reactivity, and therefore can be biased when disorders with an altered vascular state (e.g. diabetes) are studied. It is unlikely that this was the case in the disease groups which we studied. A further limitation of this method is that a proper comparison of the data obtained by different research groups is not possible, because t_0 and t_{max} depend on the chosen HN concentration, the vehicle, and the application time. Furthermore, LDF_{bas} and LDF_{max} are relative values depending on the type of laser-Doppler flowmeter used.

Comparison of TEWL measurements with t_0 values assessed by LDF, shows that there are no dramatic differences between their discriminatory values, and that both methods can discriminate between the various types of ichthyosis and the other groups. Using TEWL measurements, it was also possible to discriminate between CI and the two other types of ichthyosis. Because TEWL essentially reflects the steady state flux of a compound across the stratum corneum, and t_0 is a function of the duration of the lag phase (non-steady state) of diffusion across the stratum corneum, these two methods should not be considered as exchangeable alternatives, but rather as complementary tests. Each method reflects a different aspect of the barrier function of the skin. An advantage of TEWL measurements is that these are easier to perform and less time consuming than measurements of the vascular response to HN by LDF.

TEWL values and LDF parameters can be influenced by factors such as age, sex and atopy. Our study showed no influence of age on the TEWL values. This may be due to the relatively young age of the subjects. Only people beyond the seventh decade of life have been reported to show decreased TEWL values.[11,12] Our results are in agreement with Pinnagoda *et al.*,[11] who showed that TEWL is independent of sex, and those of Kiistala *et al.*,[15] who did not find increased TEWL values in patients with rhinitis and asthma without dermatitis. No data are available in the literature concerning the influence of age and sex on lag time (t_0). In atopic persons, diminished or absent reactivity to nicotinic acid ester has been described.[16] In our study, the patient groups were too small to be subjected to this analysis separately.

As far as we are aware, the skin barrier properties in DD and EKV have not been assessed previously. The TEWL values were increased at the alternative affected sites in the DD and EKV patients. The range of the TEWL values found on the alternative sites in the controls was wider than those found on the volar site. This is in agreement with data published on the regional variation in baseline TEWL.[11,12] Thus, in DD and EKV, both of which have autosomal dominant inheritance, only clinically affected skin shows increased TEWL, which may be due to a focal expression of the affected gene. In ADI, another autosomal inherited disease, the TEWL values were significantly increased, and t_0 values decreased, on the volar site, indicating impaired barrier function of the skin, despite the fact that some patients (3/7) had a normal-appearing skin in this location. This finding suggests that skin barrier impairment in ADI may be more closely related to the gene defect than in DD and EKV.

In conclusion, the difference in TEWL values between the various forms of ichthyosis are a further illustration of the variability of these disorders. An obvious question arising from the present study is what the major causes of the differential barrier impairment might be. Various factors such as intercellular lipid structure/phase behaviour, or the tortuosity of the intercellular pathway, may play a role. These questions are being addressed in a current study in our laboratory.

Acknowledgments

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